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Access to Unsaturated Chiral Epoxides. Part II[1]. Synthesis of a Component of the Sex Pheromone of *Phragmatobia fuliginosa*

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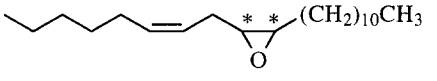
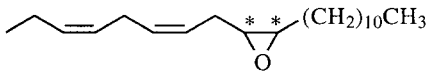
Abstract : *A general method for the synthesis of chiral cis-epoxides substituted bearing a saturated chain and an unsaturated chain is described. This method is used to synthesize both enantiomers of compound* ***1***.

Optically active epoxides are an important class of natural products encountered as sex attractants of Lepidopteran pests[2a-f], in the leukotrienes family[2g] and self-defensive substances against rice blast disease[2h]. We have previously reported a method allowing the preparation of chiral epoxides[1], substituted by two different allylic residues, and we would like to bring this work to completion with the presentation of a new general preparation of chiral cis-epoxides substituted with a saturated chain and an unsaturated long chain. A saturated chain with an eleven carbons backbone is present in several Lepidopteran sex pheromones such as **1**, **2** and **3**. The synthesis of both enantiomers of epoxide **1** will be given to examplify our strategy.



1



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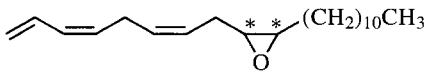

3

At the origin of this work was the observation that a leaving group adjacent to an epoxide, displays a quite low reactivity. We have shown earlier[3] that while a bromide or a tosylate in the α-position to an epoxide can be substituted by a saturated Grignard reagent in the presence of cuprous bromide, it cannot be displaced by

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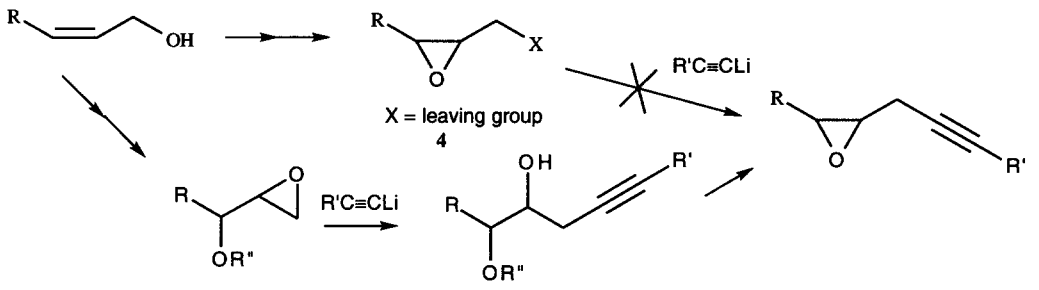
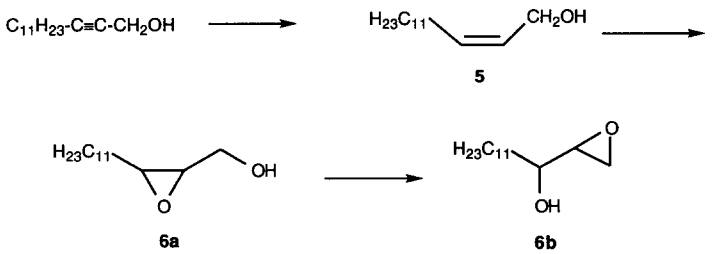
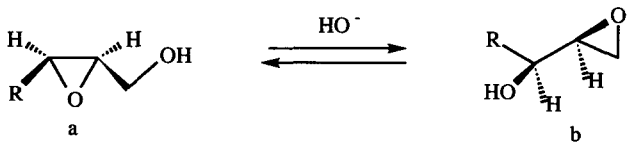
various unsaturated organometallic nucleophiles such as acetylides or lithiumalkenylcuprates. Consequently the straightforward strategy based on the use of compounds such as **4** which are easily accessible in optically active form by Sharpless epoxidation, does not work.



To circumvent the failure of this approach, we have studied the use of a more reactive terminal epoxide bearing a protected alcohol in the α-position subjected to opening by lithium acetylides. For the preparation of these kinds of compounds, the kinetically controlled epoxidation of secondary allylic alcohols is a tedious method[4] and we have studied ways starting from substituted epoxy-alcohols easily prepared in high enantiomeric excess. Compound **6a** as an example, is prepared with an e.e.> 93% from cis alcohol **5** by standard Sharpless epoxidation[4]. The transformation of **6a** into **6b** can be performed under basic conditions and is known as the Payne rearrangement[5].



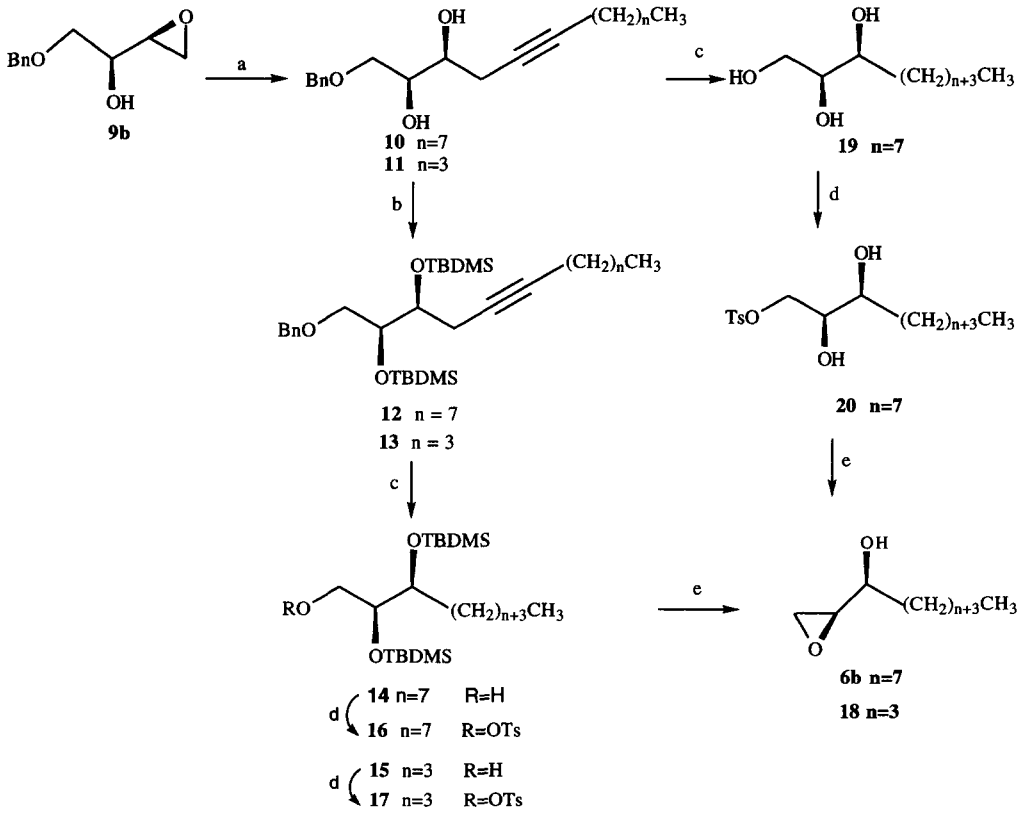
The outcome of this reaction which occurs under thermodynamic control, is also known to be highly dependent upon the structure of the epoxide and no general method can rely on this strategy. In the case of the compound **6a** the Payne rearrangement failed and several attempts to isomerise the compound **6a** in aprotic media with different bases were also unsuccessful. However examination of the rearrangement of related epoxides as reported in table 1 opened the way to an alternative but general strategy useful in our project.



entry	R-	% a	% b
6	$CH_3(CH_2)_{10}$-	100	0
7	CH_3CH_2- [8]	70	30
8	TBDMSOCH$_2$- [1]	100	0
9	$C_6H_5OCH_2$- [3]	40	60

Table 1

Compound **9** was found worthy of the focus of our attention. Its transformation into terminal epoxides **6b** or **18** by two different methods is reported in the scheme 1:



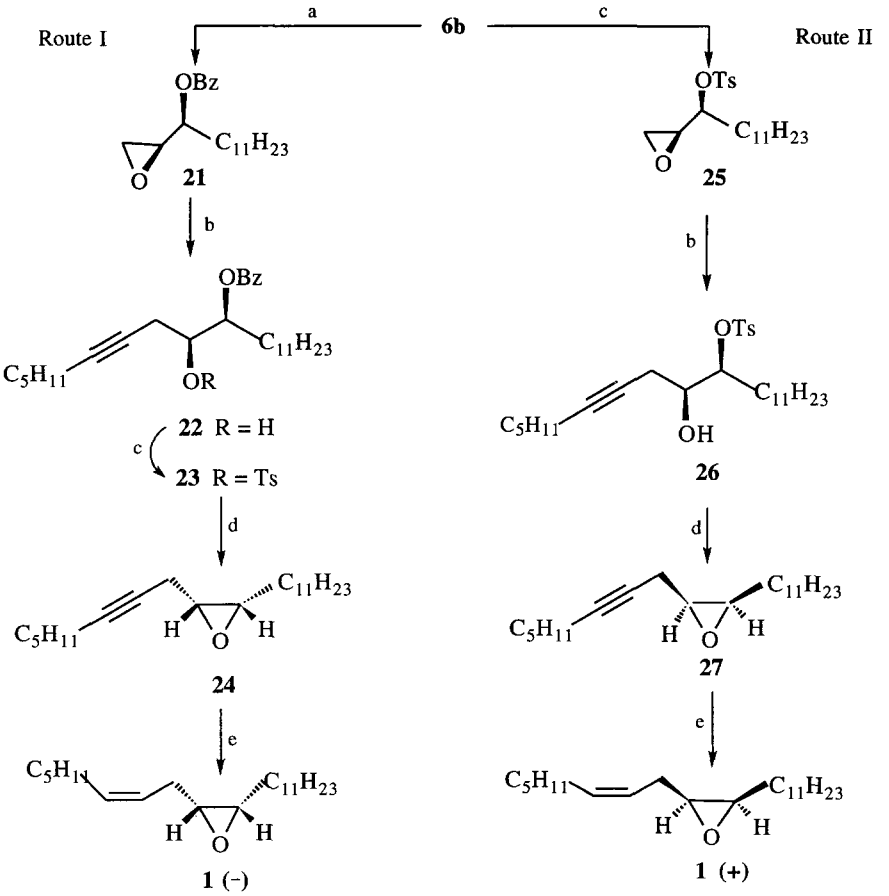
a : $CH_3(CH_2)_nC{\equiv}CLi,BF_3,(C_2H_5)_2O$,-70°C ; b : $(CH_3)_2t$-C_4H_9SiCl,DMAP,TEA ; c : H_2,Pd/C ; d : TsCl, 0°C or - 26°C, NC_5H_5
e : $(n\text{-}C_4H_9)_4NF$,THF

Scheme 1

The direct pathway through the monotosylation of triol **19** required a very accurate set-up of reaction conditions. The best yield (66 %) was obtained when the reaction was conducted at -26°C. Above -25°C the formation of ditosylate becomes significant and below -30°C unreacted triol **19** remained unchanged. To improve the yield, compounds **10** or **11** were converted into their disilylated derivatives. After hydrogenation of the triple bond, cleavage of the benzyl protecing group by hydrogenolysis and tosylation of the primary alohol, tosylates **16** or **17** were converted directly into the epoxy-alcohols **6b** and **18** while submitted to desilylation conditions (NBu_4^+,F^-). The enantiomeric purity of the resulting material was checked by HPLC on chiral phase column of the corresponding benzoates (chiral pak OT (+) column)[9].

Applications : Synthesis of a component of sex pheromone of *Phragmatobia fuliginosa*

The synthesis of both enantiomers of compound **1** which has been identified as a component of the sex pheromone of *Phragmatobia fuliginosa* is depicted on scheme 2:



a : BzCl , C_5H_5N ; b : $C_5H_{11}C{\equiv}CLi$, $BF_3,(C_2H_5)_2O$, -70°C ; c : TsCl , C_5H_5N , 0°C ; d : K_2CO_3, CH_3OH ; e : H_2 Lindlar catalyst

Scheme 2

In the route I leading to (-) enantiomer of **1**, the epoxide **6b** was first transformed into its benzoate **21**, which was submitted to reaction with heptynyllithium according to Yamaguchi's method[6], leading to **22** in good yield. After tosylation, epoxide **24** was obtained by action of potassium carbonate in methanol at room temperature on **23**. In this reaction the configuration of the carbon bearing the tosylate group is inversed by an intramolecular SN_2 process. Compound **24** was thus obtained with the 9R, 10S configuration.

A slight modification of this strategy is described on route II and allowed to prepare the 9S,10R- isomer. The same starting material **6b** is transformed into the tosylate **25** which can be opened by heptenyllithium in similar way as benzoate **21**. In this step the hydroxy-tosylate **26** is obtained and not the epoxide as we have already described[3], also pointed out by Bell[7]. We do not think that a free alkoxide exists as an intermediate but a complexed form by the Lewis acid. By catalytic hydrogenation compounds **1(-)** and **(1+)** are easily obtained from **24** and **27.**

In summary, a general method of synthesis of chiral epoxides is described. The chiral synthesis of both enantiomers of (6Z)-cis-9,10-epoxyheneicosadec-6-ene was achevied from the same intermediate compound **6b**.

Experimental Section

NMR spectra were recorded on Bruker WP200 and WM400 spectrometers in $CDCl_3$. The chemical shifts of ^1H NMR signals : δ are reported in ppm (TMS as internal standard, $\delta = 0$). Coupling constants, J, are reported in Hertz. The abbreviations : s, d, t, q, p, m and br signify : singlet, doublet, triplet, quartet, quintet, multiplet and broad respectively. IR spectra were recorded on a Perkin-Elmer using 1600 FTIR neat films on NaCl plates. Melting points were determined on a Büchi 510 apparatus and are uncorrected.

Low resolution mass spectra were recorded on a Ribermag R10-10B spectrometer under chemical ionization (NH_3) conditions high resolution mass spectra were recorded on ZAB.HFQ.VG apparatus. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 1-dm cell, in dichloromethane solutions.

All reactions were carried out under an unit atmosphere. Dry solvents were freshly distilled before used. Tetrahydrofuran (THF) was distilled from sodium-benzophenone. Dichloromethane was distilled from P_2O_5.

All reactions were monitored by thin layer chromatography carriet out on Merck silicagel plates (Ref. 5549) using 5 % ethanolic phosphomolybdic acid/heat as developing agent. Merck silicagel (Ref. 9384) was used for flash chromatography.

The synthesis of (2S,3S)1,2-epoxy-3-hydroxy-4-benzyloxybutane **9b** is described in[3]. 1-Decyne, 1-heptyne were purchased from Aldrich and distilled prior use.

Tetradec-2-en-1-ol 5

a/ Tetradec-2-yn-1-ol

To a solution of prop-2-yn-1-yloxy-tetrahydropyrane[10] (14 g, 100 mmoles) in 150 ml anhydrous tetrahydrofuran, was added slowly a solution of butyllithium (62.5 ml of 1.6N in hexane, 100 mmoles) at 0°C. After 15 min, a solution of 1-bromoundecane (23.3 g, 100 mmoles) in anhydrous hexamethylphosphotriamide (150 ml) was added at 10°C. After one night the mixture was worked up by dropwise addition of aqueous saturated ammonium chloride solution. The aqueous layer was extracted with ether (3 x 150 ml). The combined organic layers were washed with water, dried ($NaSO_4$) and concentrated. After dilution with methanol (200 ml) the crude oil was heated for two hours at 45°C with amberlist (3 g). After filtration and concentration the alcynol was distilled, b.p. = 120°C (0.01 mm Hg) ; (19 g, 90 % yield) ; m.p. = 39-40°C. ^1H NMR (200 MHz) : H_1 :

4.25 (t) ; H_4 : 2.20 (tt) ; HO : 1.90 (br s) ; H_{14} : 0.88 (t) ; $H_{5\text{-}13}$: 1.2. ^{13}C NMR (50.28 MHz) : C_1 : 51.36 ; C_2 : 78.47 ; C_3 : 86.59 ; C_4 : 18.82 ; $C_{5\text{-}11}$: 28.7-29.7 ; C_{12} : 31.99 ; C_{13} : 23.73 ; C_{14} : 14.10. IR ν_{max} : 3500. Anal. Calcd : $C_{14}H_{26}O$, C : 79.93 ; H : 12.46. Found : C : 79.61 ; H : 12.60.

b/ Tetradec-2-en-1-ol 5

A solution of tetradec-2-yn-1-ol (6.3 g, 30 mmoles) in methanol (200 ml) with quinoleine (0.1 ml) and $Pd/BaSO_4$ (0.1 g) was stirred under a hydrogen atmosphere for 3 hours. After filtration of the catalyst and concentration the product **5** was distilled, b.p. = 100°C (0.01 mmHg) ; (5.6 g, 90 % yield). ^1H NMR (200 MHz) : H_1 : 4.2 (d) ; HO : 2.9 (br s) ; H_2, H_3 : 5.5 (br m) ; H_4 : 2 (m) ; $H_{5\text{-}13}$: 1.4 ; H_{14} : 0.89 (t). ^{13}C NMR (50.28 MHz) : C_1 : 58.41 ; C_2 : 132.60 ; C_3 : 128.23 ; C_4 : 27.54 ; C_5 : 28.77 ; $C_{6\text{-}11}$: 29 ; C_{12} : 32.04 ; C_{13} : 22.82 ; C_{14} : 14.24. IR ν_{max} : 3400, 3020, 1660, 720.

(2R,3S)-2,3-epoxytetradecan-1-ol 6a

Dry methylene chloride (200ml) was cooled to - 40°C, under nitrogen, titanium isopropoxide (5.95 ml, 20 mmoles) and D(-)diethyltartrate (3.45 ml, 20 mmoles) were added sequentially. The mixture was stirred 5 min at - 40°C and **5** (4.2 g, 20 mmoles) was added dropwise. Stirring was continued for 15 min and t-butyl hydroperoxyde (10.5 ml of 3.6M in toluene, 40 mmoles) was added dropwise. The resulting mixture was maintained at - 40°C for 4 days. The mixture was worked up by dropwise addition of aqueous tartaric acid (10%, 50 ml) with vigorous stirring keeping the temperature below - 30°C. The resulting slurry was stirred for a further 60 min at - 30°C, then warmed at 20°C and stirred until the aqueous layer became clear. The layers were separated and the organic layer was washed with water and dried ($NaSO_4$). After concentration removal of tartaric ester was accomplished by stirring the crude product **6a** with 60 ml of 1N sodium hydroxyde in 150 ml of ether for 10 min, at room temperature. Usual work up afforded crude **6a** which was purified by flash chromatography (eluted with ethylacetate/cyclohexane : 20/80) ; (3.3 g, 74 % yield) ; m.p. = 60°C ; $[\alpha]_D$ = + 4 (c = 1.3). ^1H NMR (200 MHz) : H_1 : 3.7, 3.8 (dd) ; H_2, H_3 : 3.1, 3.2 (m) ; HO : 2 (br s) ; H_4 : 1.3 (m) ; H_{14} : 0.87 (t) ; $H_{5\text{-}13}$: 1.15. ^{13}C NMR (50.28 MHz) : C_1 : 60.82 ; C_2 , C_3 : 57.29 , 57.06 ; C_4 : 26.76 ; C_5 : 28.90 ; $C_{6\text{-}11}$: 29 ; C_{12} : 32.04 ; C_{13} : 22.92 ; C_{14} : 14.21. IR ν_{max} : 3400. MS m/z : M + NH_4^+ : 246 (100 %). Anal Calcd : $C_{14}H_{28}O_2$, C : 73.63 ; H : 12.36. Found : C : 73.37 ; H : 12.12.

(2S,3S)-1-benzyloxy-2,3-dihydroxytetradec-5-yne 10

To a solution of decyne (2.7 g, 20 mmoles) in anhydrous tetrahydrofuran (100 ml), was added slowly a solution of butyllithium (10.3 ml of 1.75N in hexane, 18 mmoles). After 15 min, the mixture was cooled to - 70°C, and a solution of **9b** (1 g, 5 mmoles) in anhydrous tetrahydrofuran (10 ml) was added, followed by boron trifluoride, etherate (2.75 ml, 22.5 mmoles) . The resulting mixture was maintained at - 70°C for 40 min. The mixture was worked up by dropwise addition of aqueous saturated ammonium chloride solution (80 ml) under vigorous stirring keeping the temperature at - 70°C. The mixture was allowed to warm at room temperature and the aqueous layer was extracted with ether (3 x 100 ml). The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated. Flash chromatography (ethylacetate/cyclohexane :1/1) gave pure **10** (1.4g,83%yield). $[\alpha]_D$ = - 6.4 (c = 1.4). ^1H NMR (200 MHz) : C_6H_5 : 7.34 ; $C_6H_5C\underline{H}_2$: 4.54 (s) ; H_2, H_3 : 3,8, 3,75 (m) ; H_1 = 3.62 (dd) ; HO : 3 ; H_4 : 2.44 (dt) ; $H_{.7}$: 2.12 (tt) ; H_{14} : 0.87 (t) ; $H_{8\text{-}13}$:

1.261.5. ^{13}C NMR (50.28 MHz) : C_1 : 72.62 ; C_2, C_3 : 71.17, 71.03 ; C_4 : 24.09 ; C_5, C_6 : 83.12, 75.84 ; C_7 : 18.85; $C_{8\text{-}11}$: 29 ; C_{12} : 31.93 ; C_{13} : 22.74 ; C_{14} : 14.18 ; C_6H_5-$\underline{C}H_2$: 73.75. IR ν_{max} : 3400, 1595. MS m/z : MH^+ : 333 (40 %) ; $M + NH_4^+$: 350 (80 %). Anal. Calcd. $C_{21}H_{32}O_2$, C : 75.86 ; H : 9.70. Found : C : 75.57 ; H : 9.74.

(2S,3S)-1,2,3-trihydroxytetradecane 19

A solution of **10** (0.66 g, 2 mmoles) in methanol with palladium on charcoal (10 %) was stirred under a hydrogen atmosphere for 3 hours. After filtration of the catalyst on celite and concentration, the crude product **19** was obtained quantitatively. A sample was purified by flash chromatography (ethylacetate) ; m.p. = 75°C. ^1H NMR (200 MHz) : H_1, H_2, H_3 : 3.5-3.8 ; HO : 2.3 (br s) ; H_4 : 1.5 (m) ; $H_{5\text{-}13}$: 1.3 (br s; H_4 : 0.9 (t). ^{13}C NMR (50.28 MHz) : C_1 : 64.5 : C_2, C_3 : 72.4, 74.0 ; C_4 : 33.5 ; C_5 : 25.6 ; $C_{6\text{-}11}$: 29 ; C_{12} : 31.9 ; C_{13} : 22.7 ; C_{14} : 14.0. IR ν_{max} : 3500. MS m/z : MH^+ : 247 (30%) ; $M + NH_4^+$: 264 (100 %). Anal. Calcd. $C_{14}H_{30}O_3$, C : 68.24 ; H : 12.27. Found : C : 68.19 ; H : 12.53.

(2S,3S)-1-tosyloxy-2,3-dihydroxytetradecane 20

To a solution of crude **19** (0.74 g, 3 mmoles) in dry pyridine (20 ml) at - 30°C was added p.toluenesulfonyl chloride (0.58 g, 3 mmoles). The reaction mixture was kept at - 30°C for 48 hours and then poured onto ice. The mixture was extracted with dichloromethane (3 x 50 ml) and the combined extracts were washed with 1N hydrochloric acid, dried (Na_2SO_4, K_2CO_3) and concentrated. The crude product was then purified by flash chromatography (ethylacetate/cyclohexane : 50/50) to give **20** as white solid (0.8 g, 66 % yield) ; m.p. = 76°C; $[\alpha]_D$ = - 8.8 (c = 0.85). ^1H NMR (200 MHz) : H_1 : 4.09 (dd) ; H_2, H_3 : 3.7 (m) , 3.6 (m) ; CH_3 : 2.45 (s) ; HO : 2.2 (br s) ; H_4 : 1.4 (m) ; H_{14} : 0.87 (t); $H_{5\text{-}13}$: 1.25 (br s). ^{13}C NMR (50.28 MHz) : C_1 : 70.9 ; C_2, C_3 : 71.5, 71.6 ; C_4 : 33.5 ; C_5 : 25.6 ; $C_{6\text{-}11}$: 29 ; C_{12} : 32.0 ; C_{13} : 22.8 ; C_{14} : 14.1 ; CH_3 : 21.7. IR ν_{max} : 3500, 1360, 1170. MS m/z : $M + H^+$: 401 (20 %) ; $M + NH_4^+$: 418 (100 %). Anal. Calcd. $C_{21}H_{36}O_5$, C : 62.96 ; H : 9.05. Found : C : 63.03 ; H : 8.94.

(2S,3S)-1,2-epoxy-3-hydroxytetradecane 6b

Method A : To a solution of **20** (1.2 g, 3 mmoles) in anhydrous methanol (20 ml) at room temperature, was added, in small portions, anhydrous potassium carbonate (5 equivalents). After 45 min, the solvent was removed and the mixture was directly purified by flash chromatography (ethylacetate/cyclohexane : 30/70) to give pure **6b** (1.1 g, 90 % yield) ; m.p. = 41°C. $[\alpha]_D$ = + 3.1 (c = 1.3). ^1H NMR (400 MHz) : H_3 : 3.45 (q) ; H_1 : 2.7 (dd), 2.85 (dd) ; H_2 : 2.95 (m) ; HO: 2 (br s) ; H_4 : 1.6 (m) ; $H_{5\text{-}13}$: 1.26 ; H_{14} : 0.88 (t). ^{13}C NMR (50.28 MHz) : C_1 : 45.2 ; C_2 : 55.5 ; C_3 : 71.6 ; C_4 : 32.0 ; C_5 : 25.4 ; $C_{6\text{-}11}$: 29 ; C_{12} : 34.5 ; C_{13} : 22.7 ; C_{14} : 14.1. IR ν_{max} : 3400. MS m/z : $M + NH_4^+$: 246 (100 %). Anal. Calcd. $C_{14}H_{28}O_2$, C : 73.65 ; H : 12.36. Found : C : 73.53 ; H : 12.53.

Method B : To a solution of **16** (1.2 g, 2 moles) in anhydrous tetrahydrofuran (20 ml), at room temperature, was added, dropwise a solution of tetra n-butylammonium fluoride (9 ml of 1M THF). After 3 hours the reaction mixture was diluted with a saturated aqueous ammonium chloride solution (25 ml) and extracted with ether (3 x 50 ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated to give **6b**. Flash

chromatography (ethylacetate/cyclohexane : 30/70) gave pure **6b** identical to the compound obtained by method A.

(2S,3S)-1-benzyloxy-2,3-dihydroxydec-5-yne 11

The compound **11** was prepared from hexyne by the same procedure and on the same scale as used for **10** (0.4 g, 76 % yield) ; m.p. = 71°C. $[\alpha]_D$ = - 8.5 (c = 0.8). ^{1}H NMR (200 MHz) : C_6H_5 : 7.34 (s) ; C_6H_5-$C\underline{H}_2$: 4.58 (s) ; H_1, H_2, H_3 : 3.90-3.63 (m) ; H_4 : 2.44 (dt) ; H_7 : 2.16 (tt) ; H_8, H_9 : 1.44 (br s) ; H_{10} : 0.94 (t) ; HO : 2.8, 2.6. ^{13}C NMR (50.28 MHz) : C_1 : 72.6 ; C_2, C_3 : 71.1, 71.0 ; C_4 : 24.0 ; C_7 : 18.5 ; C_8 : 31.1 ; C_9 : 22.0 ; C_{10} : 13.6 ; C_6H_5-$\underline{C}H_2$: 73.7. IR ν_{max} : 3400. MS m/z : M + H^+ : 277 (30 %) ; M + NH_4^+ : 294 (100 %). Anal. Calcd $C_{17}H_{24}O_3$, C : 73.88 ; H : 8.75. Found : C : 73.48 ; H : 8.92.

(2S,3S)-1-benzyloxy-2,3-di(t-butyldimethylsilyloxy)tetradec-5-yne 12

To a solution of **10** (0.66 g, 2 mmoles) in anhydrous dichloromethane, 4-Ndimethylaminopyridine (0.2 g), t-butyldimethylsilylchloride (1 g) and triethylamine (2 ml) were added sequentially. The mixture was stirred 5 days at room temperature and worked up by addition of aqueous saturated ammonium chloride solution (40 ml) under vigorous stirring. The aqueous layer was extracted with dichloromethane (3 x 50 ml). The organic layer was washed with 1N hydrochloric acid till neutrality, dried ($MgSO_4$) and concentrated. Flash chromatography (ethylacetate/cyclohexane : 10/90) gave pure **12** (1 g, 92 % yield). $[\alpha]_D$ = - 16.8 (c = 0.86). ^{1}H NMR (200 MHz) : H_1 : 3.4, 3.70 (dd) ; H_2, H_3 : 3.96 , 3.82 (m) ; H_4 : 2.4 (m) ; H_7 : 2.14 (tt) ; $H_{8\text{-}13}$: 1.29-1.45 ; C_6H_5-$C\underline{H}_2$: 4.52 (s) ; t.C_4H_9, H_{14} : 0.9 ; CH_3-Si : 0.11 (s). ^{13}C NMR (50.28 MHz) : C_1 : 71.6 ; C_2, C_3, C_6H_5-$\underline{C}H_2$: 73.2, 73.3, 73.4 ; C_4 : 22.8 ; C_5, C_6 : 81.5, 78.0 ; C_7 : 19.0 ; $C_{8\text{-}11}$: 29 ; C_{12} : 32 ; C_{13} : 22.0 ; C_{14} : 14.2 ; $\underline{C}H_3$-C : 25.9 ; CH_3-$\underline{C}$: 18.2 ; CH_3-Si : - 4.2. IR ν_{max}: 1253, 836. MS m/z : M + H^+ : 561 (100 %).

(2S,3S)-1-benzyloxy-2,3-di(t-butyldimethylsilyloxy)dec-5-yne 13

The compound **13** was synthesized according to the same procedure and on the same scale as used for **12** (0.7 g, 69 % yield) ; $[\alpha]_D$ = - 20.4 (c = 1.2). ^{1}H NMR (200 MHz) : H_1 : 3.4, 3.6 (ddd) ; H_2 : 3.9 (q) ; H_3 : 3.7 (br m) ; H_4 : 2.6, 2.3 (ddt) ; H_7 : 2.1 (tt) ; $H_{8,9}$: 1.3 ; H_{10}, CH_3-C : 0.9 ; CH_3-Si : 0.1 (s) ; C_6H_5 : 7.32 ; C_6H_5-$C\underline{H}_2$: 4.53 (s). ^{13}C NMR (50.28 MHz) : C_1 : 71.65 ; C_2, C_3 : 73.34, 73.50 ; C_4 : 22.72 ; C_5, C_6 : 78.11, 77.77 ; C_7 : 18.68; C_8 : 31.23 ; C_9 : 22.13 ; C_{10} : 13.71 ; CH_3-Si : - 4.64 ; $\underline{C}H_3$-C : 25.97; CH_3-$\underline{C}$: 18.20 ; C_6H_5-$\underline{C}H_2$: 73.50. IR ν_{max} : 1253, 83 H^+ : 505 (100 %).

(2S,3S)-1-hydroxy-2,3-di(t-butyldimethylsilyloxy)tetradecane 14

A solution of **10** (1.1 g, 2 mmoles) in methanol (50 ml) with palladium on charcoal (10 %) was stirred under a hydrogen atmosphere for 2 hours. After filtration of the catalyst and concentration the crude product **14** was obtained quantitatively (0.9 g). A sample was purified by flash chromatography (ethylacetate/cyclohexane : 20/80). $[\alpha]_D$ = - 27 (c = 1.9). ^{1}H NMR (200 MHz) : H_1, H_2, H_3 : 3.5-3.8 ; H_4, t.C_4H_9 : 0.90 ; H_4 : 1.70 (m) ; $H_{5\text{-}13}$: 1.2; CH_3-Si : 0.1 ; HO :2.4. ^{13}C NMR (50.28 MHz) : C_1 : 63.33 ; C_2 , C_3 : 73.89, 75.53 ; C_4 : 32.04 ; C_5 : 26.71 ; $C_{6\text{-}11}$: 29 ; C_{12} : 30.57 ; C_{13} : 22.81 ; C_{14} : 14.22 ; CH_3-$\underline{C}$: 18.08 ; $\underline{C}H_3$-C : 25.88 ;

CH_3-Si : - 4.57. IR ν_{max}: 3441, 1256, 836. MS m/z : M+ H^+ : 475 (100 %).

(2S,3S)-1-hydroxy-2,3-di(t-butyldimethylsilyloxy)decane 15

This compound was synthesized according to the same procedure and on the same scale used for **14** (0.8 g, quantitative yield). $[\alpha]_D$ = - 28.6 (c = 1.8). ^1H NMR (200 MHz) : H_1, H_2, H_3 : 3.5-3.8 (b m) ; HO : 2.5 ; H_4 : 1.7 (d t) ; $H_{5\text{-}9}$: 1.2 ; CH_3-C, H_{10} : 0.9; CH_3-Si : 0.1. ^{13}C NMR (50.28 MHz) : C_1 : 63.38 ; C_2, C_3 : 75.59, 74.07 ; C_4 : 26.75 ; C_5 : 30.71 ; C_6 : 29.79 ; C_7 : 29.36 ; C_8 : 31.98; C_9 : 22.80 ; C_{10} : 14.21 ; $\underline{C}H_3$-C : 25.94 ; CH_3-$\underline{C}$: 18.13 ; CH_3-Si : - 4.51. IR ν_{max} : 3464, 1256, 836.

(2S,3S)-1-tosyloxy-2,3-di(t-butyldimethylsilyloxy)-tetradecane 16

To a solution of **14** (1.4 g, 3 mmoles) in dry pyridine (15 ml) at 0°C was added p-toluenesulfonylchloride (0.6 g, 6 mmoles). The reaction mixture was kept at 0°C for 16 h, and then poured onto ice. The mixture was extracted with dichloromethane (3 x 50 ml) and the combined extracts were washed with 1N hydrochloric acid, dried (Na_2SO_4, K_2CO_3) and concentrated. The crude product was then purified by flash chromatography (ethylacetate/cyclohexane : 10/90) to give **16** (1.6 g, 87.5 % yield). $[\alpha]_D$ = - 33 (c = 0.8). ^1H NMR (200 MHz) : H_1 : 3.8, 4.2 (dd) ; H_2, H_3 : 3.5 (m), 3.8 (m) ; $C\underline{H}_3$-C_6H_4 : 2.45 (s) ; H_{14}, t.C_4H_9 : 0.8 ; CH_3-Si : 0.1. ^{13}C NMR (50.28 MHz) : C_1 : 71.80 ; C_2, C_3 : 73.67, 73.95 ; C_4 : 32.04 ; C_5 : 26.59 ; $C_{6\text{-}11}$: 29 ; C_{12} : 30.70 ; C_{13} : 22.80 ; C_{14} : 14.21 ; CH_3-$\underline{C}$: 18.08 ; $\underline{C}H_3$-C : 25.84 ; CH_3-Si : - 4.57. IR ν_{max} : 1256, 1178, 836. MS m/z : MH^+ : 622 (60 %) ; M + NH_4^+ : 646 (100 %)

(2S,3S)-1-tosyloxy-2,3-di(t-butyldimethylsilyloxy)decane 17

This compound was synthesized according to the same procedure and on the same scale used for **16** (0.5 g, 87 % yield). $[\alpha]_D$ = - 35 (c = 1.2). ^1H NMR (400 MHz) : H_1, 4.15, 3.85 (dd) ; H_2 : 3.8 (ddd) ; H_3 : 3.5 (ddd) ; H_4 : 1.5 ; $H_{5\text{-}9}$: 1.26 ; H_{10} , CH_3-C : 0.81 ; $C\underline{H}_3$-C_6H_4 : 2.45 (s) ; CH_3-Si : 0.09 (s). ^{13}C NMR (50.28 MHz) : C_1 : 71.79 ; C_2, C_3 : 73.66, 73.96 ; C_4 : 26.59 ; C_5 : 30.71 ; C_6 : 29.28 ; C_7 : 29.56 ; C_8 : 31.92; C_9 : 21.70 ; C_{10} : 14.16 ; $\underline{C}H_3$-C : 25.84 ; CH_3-$\underline{C}$: 17.99 ; CH_3-Si : - 4.75 ; $\underline{C}H_3$-C_6H_4 : 21.70. IR ν_{max} : 1257, 1178, 837. MS m/z : MH^+ : 573 (30 %) ; M + NH_4^+ : 590 (70 %)

(2S,3S)-1,2-epoxy-3-hydroxydecane 18

This compound was synthesized according to the same procedure and on the same scale used for **6b** (0.3 g, 87 % yield). $[\alpha]_D$ = + 1.7 (c =1.2). ^1H NMR (400 MHz) : H_1 : 2.8, 2.7 (m) ; H_2 : 2.9 (m) ; H_3 : 3.4 (m) ; H_4 : 1.59 (b t) ; $H_{5\text{-}9}$: 1.4 ; H_{10} : 0.91 (t) ; HO : 2. ^{13}C NMR (50.28 MHz) : C_1 : 45.26 ; C_2 : 55.51 ; C_3 : 71.63 ; C_4 : 34.56 ; C_5 : 31.90 ; C_6 : 29.69 ; C_7 : 29.30 ; C_8 : 31.90 ; C_9 : 22.74 ; C_{10} : 14.16. IR ν_{max} : 3422. MS m/z : M + NH_4^+ : 190 (100 %).

(2S,3S)-1,2-epoxy-3-benzyloxytetradecane 21

To a solution of **6b** (0.45 g, 2 mmoles) in dry pyridine (10 ml), at room temperature, was added benzoyl chloride (0.23 ml, 2 mmoles). After 15 min the reaction mixture was diluted with water (20 ml) and

extracted with methylene chloride (3 x 40 ml). The combined organic extracts were washed with 1N hydrochloric acid still neutrality and dried ($NaSO_4$). After filtration and concentration, the crude product **21** was then purified by flash chromatography (ethylacetate/cyclohexane : 20/80) (0.6 g, 92 % yield). $[\alpha]_D$ = - 4 (c = 1.8).e.e.>93% (H.P.L.C., chiral pak OT (+) column). ^1H NMR (200 MHz) : H_1 : 2.64 (dd), 2.66 (dd) ; H_2 : 3.20 (m) ; H_3 : 5.02 (q) ; H_4 : 1.79 (tt) ; $H_{5\text{-}13}$: 1.23 ; H_{14} : 0.86 (t). ^{13}C NMR (50.28 MHz) : C_1 : 44.85 ; C_2 : 53.16 ; C_3 : 74.31 ; C_4 : 25.27 ; $C_{5\text{-}11}$: 29 ; C_{12} : 31.96 ; C_{13} : 22.73 ; C_{14} : 14.15 ; C=O : 165.96. IR ν_{max} : 3060, 1720. MS m/z : $M + H^+$: 333 (100 %) ; $M + NH_4^+$: 350 (10 %).

(9S,10S)-9-hydroxy-10-benzyloxyheneicosadec-6-yne 22

To a solution of heptyne (0.82 ml, 6 mmoles) in anhydrous tetrahydrofuran (50 ml) was added slowly a solution of butyllithium (2.5 ml of 1.6N in hexane, 4 mmoles). After 20 min the mixture was cooled to - 70°C, a solution of **21** (0.66 g, 2 mmoles) in anhydrous tetrahydrofuran (15 ml) was added, followed by boron trifluoride, etherate (0.36 ml, 3 mmoles). The resulting mixture was maintained at - 70°C for 15 min. The mixture was worked up by dropwise addition of aqueous saturated ammonium chloride solution (30 ml) with vigorous stirring while maintaining the temperature at - 70°C. After warming to room temperature, the aqueous layer was extracted with ether (3 x 50 ml) and the combined organic layers were washed with water, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (ethylacetate/cyclohexane : 20/80) giving **22** (0.74 g, 86 % yield). $[\alpha]_D$ = + 3.3 (c = 1.3). ^1H NMR (200 MHz) : H_1, H_{21} : 0.9 (t) ; H_5 : 2.09 (m) ; H_8 : 2.49 (d t) ; H_9 : 3.85 (m) ; H_{10} : 5.25 (m) ; $H_{2\text{-}4,\ 12\text{-}20}$: 1. ^{13}C NMR (50.28 MHz) : C_1, C_{21} : 14.08, 14.21 ; C_2, C_{20} : 22.79, 22.31 ; C_3, C_{19}, C_{11} : 32.02, 31.28, 30.21 ; C_5 : 18.81 ; C_6, C_7 : 83.77, 75.17 ; C_8, C_{12} : 25.33, 24.65 ; C=O : 166.49 ; $C_{13\text{-}18}$: 29. IR ν_{max} : 3400, 1725. MS m/z : $M + H^+$: 429 (50 %).

(9S,10S)-9-tosyloxy-10-benzyloxyheneicosadec-6-yne 23

To a solution of **22** (0.85 g, 2 mmoles) in dry dichloromethane (15 ml), at room temperature, was added dry triethylamine (0.15 ml) and 4N-dimethylaminopyridine (0.15 g). The resulting mixture was cooled at 0°C, p-toluenesulfonylchloride (0.8 g, 4 mmoles) was added. After one hour, the reaction mixture was kept at 25°C for 48 hours, then poured onto ice. The mixture was extracted with ether (3 x 20 ml) and the combined extracts were washed with 1N hydrochloric acid, dried ($NaSO_4$) and concentrated. The crude product was then purified by flash chromatography (ethylacetate/cyclohexane : 20/80) to give pure **23** (1 g, 86 % yield). $[\alpha]_D$ = + 27.9 (c = 0.86) ; m.p. = 32°C. ^1H NMR (400 MHz) : $H_{1,\ 21}$: 0.9 (t) ; $H_{2\text{-}4,\ 12\text{-}20}$: 1.1-1.5 ; H_5 : 2.05 (tt) ; H_9 : 4.8 ; H_{10} : 5.45 ; H_8 : 2.75 (ddt) ; $C\underline{H}_3\text{-}C_6H_4$: 2.42 (s). ^{13}C NMR (100 MHz) : $C_{1,\ 21}$: 14.11, 14.25 ; C_2, C_{20} : 22.32, 22.81 ; C_3, C_{19}, C_{11} : 32.03, 31.17, 31.58 ; C_5 : 18.77; C_9 : 80.46 ; C_{10} : 73.02 ; C_6, C_7 : 84.07, 74.37 ; C_4, $C_{13\text{-}18}$: 29 ; $\underline{C}H_3\text{-}C_6H_4$: 21.77 ; C_8, C_{12} : 25.14, 25.34 ; C=O : 165. IR ν_{max} : 1720, 1177. MS m/z : $M + NH_4^+$: 600 (100 %) ; $M + H^+$: 583 (15 %).

(9R,10S)-9,10-epoxyheneicosadec-6)-yne 24

To a solution of **23** (0.58 g, 1 mmole) in anhydrous methanol (20 ml) at room temperature, was added, in small portions, anhydrous potassium carbonate (5 equivalents). After 30 min, the solvent was removed and the mixture was directly purified by flash chromatography (ethylacetate/cyclohexane : 10/90) to give pure **24**

(0.18g,60%yield).$[\alpha]_D$ = - 26.2 (c = 1.2). ^{1}H NMR (400 MHz) : H_1, H_{21} : 1.33 (q) ; H_4, $_{9\text{-}20}$: 1.2-1.6 ; H_4 : 2.2 (ddt) ; H_5 : 2.17 (tt) H_8 : 2.6-2.5 (ddt) ; H_9 : 3.1 (m) ; H_{10} : 2.9 (m). ^{13}C NMR (50.28 MHz) : C_1, C_{21} : 14.23, ; C_2, C_{20} : 22.33, 22.80 ; C_3, C_{19} : 32.04, 31.19 ; C_5 : 18.91 ; C_6, C_7 : 82.63, 74.98 ; C_9, C_{10} : 57.23, 55.58 ; C_8 : 26.61 ; $C_{13\text{-}18}$: 29. MS m/z : M + H$^+$: 307 (100 %) ; M + NH_4^+ : 324 (30 %).

(6Z,9R,10S)-9,10-epoxyheneicosadec-6-ene 1 (-)

A solution of **24** (0.3 g, 1 mmole) in methanol (20 ml) with Lindlar catalyst (10 mg) was stirred under a hydrogen atmosphere for 1 hour. After filtration of the catalyst and concentration, the residue was purified by flash chromatography (ethylacetate/cyclohexane : 10/90) to give pure **1** (-) (0.3 g quantitative yield). $[\alpha]_D$=-4 (c= 1.2). ^{1}H NMR (400 MHz) : H_9, H_{10} : 2.9 (m) ; H_6, H_7 : 5.5, 5.4 (m) ; H_8 : 2.4-2.2 (m) ; H_1, H_{21} : 0.9 (m) ; H_5 : 2.0 (m) ; $H_{9\text{-}20}$: 1.3. ^{13}C NMR (50.28 MHz) : C_7, C_6 : 132.8, 124.5 ; C_9, C_{10} : 56.67, 56.13 ; C_1, C_{21} : 14.22, 14.16 ; C_2, C_{20} : 22.67, 22.80 ; C_3, C_{19} : 32.03, 31.61 ; C_5, C_8 : 27.90, 27.64 ; C_{11} : 26.33. IR ν_{max} : 3030.

(2S,3S)-1,2-epoxy-3-tosyloxytetradecane 25

To a solution of **6b** (0.9 g, 4 mmoles) in dry pyridine (15 ml) at 0°C, was added p. toluenesulfonylchloride (1.5 g, 8 mmoles). The reaction mixture was kept at 0°C for 2 days, and then poured onto ice. The mixture was extracted with dichloromethane (3 x 40 ml) and the combined extracts were washed with 1N hydrochloric acid, dried ($NaSO_4$, K_2CO_3) and concentratred. The crude product was then purified by flash chromatography (ethylacetate/cyclohexane : 10/90) to give **25** (1.2 g, 85 % yield). m.p. = 72°C ; $[\alpha]_D$ = + 4.3 (c = 0.7). ^{1}H NMR (200 MHz) : H_1 : 2.77 (dd), 2.64 (dd) ; H_2 : 3.08 (m) ; H_3 : 4.36 (q) ; H_4 : 1.7 (br m) ; H_{14} : 0.89 (t) ; $\underline{C}H_3$-C_6H_4 : 2.46 (s) ; $H_{5\text{-}13}$: 1.2. ^{13}C NMR (50.28 MHz) : C_1 : 44.96 ; C_2 : 52.84 ; C_3 : 83.56 ; C_{14} : 14.24 ; C_{13} : 22.81 ; C_{12}, C_5 : 32.03, 31.96 ; $\underline{C}H_3$-C_6H_4 : 21.79 ; C_4 : 24.94 ; $C_{6\text{-}11}$: 29. IR ν_{max} : 3050, 1600, 1350, 1178.

(9S,10S)-9-hydroxy-10-tosyloxyheneicosadec-6-yne 26

This compound was synthesized according to the same procedure and on the same scale used for **22** (0.5 g, 80 % yield). $[\alpha]_D$ = - 7 (c = 1.1). ^{1}H NMR (200 MHz) : H_1, H_{21} : 0.83 (m) ; H_5 : 2.09 (tt) ; H_8 : 2.29 (dt) ; HO : 2.3 (br s) ; $C\underline{H}_3$-C_6H_4 : 2.39 (s) ; H_9 : 3.75 (m); H_{10} : 4.65 (m); $H_{9\text{-}20}$: 1.2. ^{13}C NMR (50.28 MHz) : C_1, C_{21} : 14.06, 14.19 ; C_5 : 18.81 ; C_2, C_{20} : 22.31, 22,78 ; C_3, C_{19}, C_{11} : 32.02, 31.20, 30.68 ; C_6, C_7 : 83.76, 74.96 ; C_8 : 23.98 ; C_9 : 70.59 ; C_{10} : 84.87 ; CH_3 : 21.72.9 IR ν_{max} : 3400, 1177.

(9S,10R)-9,10-epoxyheneicosadec-6-yne 27

This compound was synthesized according to the same procedure and on the same scale used for **24** (0.2 g, 70 % yield). $[\alpha]_D$ = + 25 (c = 1.1). This material was spectroscopically and chromatographically identical to **24**.

(6Z,9S,10R)-9,10-epoxyheneicosadec-6-ene 1 (+)

This compound was synthesized according to the same procedure and on the same scale used for **1** (-) (0.3 g, quantitative yield). $[\alpha]_D$ = + 5 (c = 0.9) {Lit. $[\alpha]_D$ = + 9.4 (c = 0.55, $CHCl_3$)[2c], $[\alpha]_D$ = + 5.5 (c = 5.00, CCl_4)[2d], $[\alpha]_D$ = + 6.8 (c = 5.05, CCl_4)[2b]}. This material was spectroscopically and chromatographically identical to (6Z,9R,10S) **1** (-).

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